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Long-Term Safety Outcomes in Patients with Hematological Malignancies Undergoing Autologous Hematopoietic Stem Cell Transplantation Treated with Palifermin to Prevent Oral Mucositis

Patrick J. Stiff [1,*], Mika Leinonen [2,3], Torbjörn Kullenberg [2], Mattias Rudebeck [2], Maarten de Chateau [2], Ricardo Spielberger [4,5]

[1] *Cardinal Bernardin Cancer Center, Division of Hematology and Oncology, Department of Medicine, Loyola University Medical Center, Maywood, Illinois*
[2] *Sobi, SE-112 76, Stockholm, Sweden*
[3] *4Pharma AB, Stockholm, Sweden*
[4] *City of Hope Department of Hematology and Hematopoietic Cell Transplantation, Los Angeles, California*
[5] *Southern California Permanente Medical Group, Los Angeles, California*

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A B S T R A C T

The purpose of our study was to compare long-term safety outcomes (overall survival, disease progression, and incidence of secondary malignancies) between palifermin and placebo in the prevention of oral mucositis in patients with hematological malignancies undergoing autologous hematopoietic stem cell transplantation (HSCT). Patients were enrolled between 1997 and 2005 into 4 phase I to III studies (3 double-blind placebo-controlled and 1 open-label) conducted at 31 sites in Australia, Europe, and the United States. Survival outcomes (overall survival, progression-free survival) were compared using hazard ratios (HRs) estimated with a Cox model that included treatment group, baseline age, disease type, Eastern Cooperative Oncology Group performance status, country, and presence of prior radiotherapy as covariates. The incidence of secondary malignancies was compared with a chi-square test. A total of 672 patients were randomized into the studies (428 palifermin and 244 placebo). The median follow-up time for subjects alive at last visit was 7.9 years (range, .1 to 14.9) for palifermin and 8.8 years (range, .1 to 14.8) for placebo. Palifermin-treated patients had overall survival (HR, 1.01; 95% confidence interval [CI], .78 to 1.31; $P = .921$) and progression-free survival times (HR, 1.04; 95% CI, .83 to 1.31; $P = .733$) that were comparable with placebo-treated patients. Secondary malignancies were reported by 13% of palifermin-treated patients versus 11% of placebo patients ($P = .477$). Breakdown into secondary hematological malignancies (7% versus 6%) or solid tumors (6% versus 6%) did not suggest any differences between the treatment groups. After a follow-up of up to 15 years, comparable long-term safety outcomes (overall survival, progression-free survival, and incidence of secondary malignancies) were observed for palifermin- and placebo-treated patients undergoing autologous HSCT.

INTRODUCTION

Treatments for malignancies with chemotherapeutic agents and/or radiotherapy are becoming increasingly effective but are associated with short- and long-term side effects, including complications such as oral mucositis (OM) [1]. OM typically appears 7 to 14 days after the start of chemotherapy or with radiotherapy at a cumulative tissue dose of 15 Gy to 20 Gy of standard fractionated radiation therapy [2]. The incidence of ulcerative OM ranges between 20% and 80%, depending on the cancer treatment [3,4], but patients undergoing chemoradiotherapy for hematological malignancies have an incidence closer to 100% [5]. Clinical features of OM include erythema, ulceration, and pseudomembrane formation, which can lead to pain, difficulty in swallowing and chewing food, and increased risk of

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* Correspondence and reprint requests: Patrick J. Stiff, MD, Loyola University Chicago, 2160 S. First Avenue, Cardinal Bernardin Cancer Center, Building 112, Room 255, Chicago, IL 60153.
E-mail address: pstiff@lumc.edu (P.J. Stiff).

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infections [6]. Severe symptomatic OM can also contribute to therapy interruption and increased antibiotics and narcotics use, hospitalization time, and overall treatment cost [6].

Over the years, various drugs and methods have been investigated to treat and prevent OM. For patients undergoing hematopoietic stem cell transplantation (HSCT) for treatment of chemosensitive malignancies, such as multiple myeloma and non-Hodgkin and Hodgkin lymphomas, successful therapies include oral cryotherapy [7], low-level light laser therapy [8], and palifermin [1,9]. Palifermin (Kepivance, Swedish Orphan Biovitrum AB [Sobi], Stockholm, Sweden) has been shown to reduce the incidence and duration of severe OM in patients undergoing HSCT, improve swallowing problems and nutrition, and decrease length of hospital stay and narcotic opioid use compared with placebo [10-14]. However, palifermin had no impact on rates of infection, dietary intake, or time to engraftment [12]. Overall, palifermin has been shown to be well tolerated and safe for patients in shorter follow-up studies [5,10,15,16].

Palifermin, which is an N-truncated human keratinocyte growth factor (KGF) produced by recombinant DNA technology, has improved protein stability over endogenous human KGF [17]. It acts physiologically on cells that express the KGF receptor, stimulating their proliferation, differentiation, and survival [17]. Unlike cells of mesenchymal origin, cells of the haematopoetic lineage do not express the KGF receptor, and the administration of pharmacologic doses of palifermin for the prevention or treatment of OM in patients with hematologic malignancies is not suspected to have adverse effects on the promotion of secondary haematological malignancies. However, the incidence of secondary malignancies and mortality because of malignancies of epithelial cell origin could potentially be higher in patients treated with palifermin.

Regardless, patients undergoing high-dose chemo/radiotherapy and autologous HSCT are at significant risk for developing a secondary malignancy [18], and because palifermin is intended as a supportive care agent, it is important to evaluate its effects on long-term safety outcomes. The objective of this study was to compare long-term safety outcomes (overall survival, progression-free survival, and incidence of secondary malignancies) of palifermin versus placebo when used to prevent OM in patients with hematological malignancies undergoing autologous HSCT.

PATIENTS AND METHODS

Study Design and Participants

Patients with hematological malignancies undergoing high-dose chemotherapy with or without total body irradiation followed by autologous HSCT were initially enrolled in 4 phase I to phase III studies (3 double-blind placebo-controlled studies [5,15,16] and 1 open-label study (unpublished data)) conducted at 31 sites in Australia, Europe, and the United States between 1997 and 2005 (Table 1). Patients were eligible for participation in a long-term follow-up study if they had received at least 1 dose of investigational product regardless of treatment group assignment in any of the 4 parent studies. All subjects were required to give written informed consent to be enrolled in the parent study as well as in the follow-up study. Patients were followed from the beginning of the above mentioned clinical studies to the time of the study closure (2012).

Analytic Methods

Demographic data, subject baseline characteristics, and exposure to investigational product were collected in the parent studies. Demographic and baseline characteristics were compared between treatment groups using either a *t*-test (continuous variables), a chi-square test (categorical variables), or Fisher's exact test (categorical variables with small cell size).

Survival status (dead or alive, disease progression or no progression) of all treated patients were included to their last follow-up time, whether in the parent study or in the follow-up study. Data on secondary malignancies were available only for the patients enrolled in the follow-up study and up until their last follow-up time.

Survival outcomes (overall survival and progression-free survival), beginning from the date of first palifermin infusion, were compared using hazard ratios (HRs) estimated using a Cox model that included treatment group, baseline age, disease type (Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, leukemia), Eastern Cooperative Oncology Group performance status, country, and presence of prior radiotherapy as covariates. Because the covariates included in the Cox models were not predefined, stepwise multivariate Cox models were used as an initial step to select the covariates to be used in the final Cox models. All demographic and baseline characteristics collected in the studies were included in this process as potential explanatory factors. Forward selection steps followed by backward elimination steps were used on a 2-sided significance level of .10 for both selection and elimination. For time to cancer-related death, deaths preceded by disease progression or development of a secondary malignancy were classified as events, whereas deaths from other reasons were censored. For time to non–cancer-related deaths, death preceded by disease progression or development of a secondary malignancy were censored, whereas death due to other reasons were classified as events.

In addition to the HR estimates calculated with the adjusted Cox model, the survival outcomes were described with unadjusted Kaplan-Meier plots. Incidence of secondary malignancies was compared using a chi-square test.

RESULTS

A total of 672 patients were randomized to the parent studies, with 662 patients receiving at least 1 dose of palifermin or placebo (Figure 1). A total of 543 patients participated in the long-term follow-up study and were followed for secondary malignancies. However, data from all 662 patients were used for the analysis of overall survival and progression-free survival times.

Overall median follow-up time among the patients who were alive at the last contact was 8.2 years (range, .1 to 14.9) for a total of 3557 cumulative follow-up years. Median follow-up time was 7.9 years (range, .1 to 14.9) for patients in the palifermin group and 8.8 years (range, .1 to 14.8) for patients in the placebo group (Table 2). The mean age of patients was 45 years (Table 3), and the majority were male (63%), Caucasian (84%), diagnosed with non-Hodgkin lymphoma (71%), and had an Eastern Cooperative Oncology Group performance status of 0 (70%). Compared with the placebo group, more patients in the palifermin group were diagnosed with non-Hodgkin lymphoma (73.9% versus

Table 1
Study Descriptions

Study	Phase	Randomization (Palifermin:Placebo)	Design	Study Endpoints
1 [15]	I/II	2:1	Double-blind, multicenter, dose-escalation	Safety and tolerability of palifermin
2 [16]	II	2:1	Double-blind, multicenter	Efficacy and safety of palifermin
3 [5]	III	1:1	Double-blind, multicenter	Efficacy and safety of palifermin
4	I	N/A	Open-label, single-center	PK profile of palifermin

PK indicates pharmacokinetic.

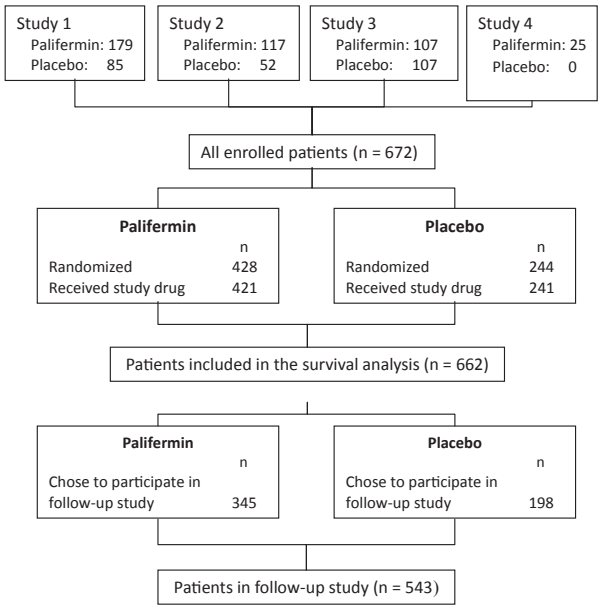

Figure 1. Patient disposition.

66.0%; $P = .031$) and fewer patients were diagnosed with Hodgkin lymphoma (18.3% versus 24.5%; $P = .058$). Patients were exposed to 5 μg/kg to 180 μg/kg of palifermin, which was administered in 1 to 6 daily doses. Average daily dose level was <60 μg/kg in 14%, 60 μg/kg in 68%, and >60 μg/kg in 18% of the patients. Patients with prior transplantation were excluded from the parent studies, with the exception of second transplantations in tandem transplantations. Only 1 patient enrolled received a tandem transplantation regimen, and palifermin was used only during the second transplantation.

Comparable overall survival times were seen in patients treated with palifermin versus placebo (HR, 1.01; 95% confidence interval [CI], .78 to 1.31; $P = .921$) (Figure 2A). Progression-free survival times were also comparable (HR, 1.04; 95% CI, .83 to 1.31; $P = .733$) (Figure 2B) between the treatment groups. In addition, the HRs were comparable between the 2 treatment groups when analyzed by disease subgroup (Figure 3). Finally, the placebo and palifermin groups showed comparable time to cancer-related death (HR, 1.03; 95% CI, .78 to 1.38) as well as comparable time to non–cancer-related death (HR, .95; 95% CI, .54 to 1.67). Differences in palifermin dose levels (<60 μg/kg/day, 60 μg/kg/day, and >60 μg/kg/day) had no significant effect on overall survival ($P = .258$) or progression-free survival ($P = .161$) when included as an additional covariate in the Cox model.

Overall, the incidence of secondary malignancies (Table 4) was comparable between patients treated with palifermin or placebo (13% versus 11%; $P = .477$). Comparable results were also observed between patients treated with palifermin or placebo when secondary malignancies were further characterized as hematological malignancies (7% versus 6%) or solid tumors (6% versus 6%) or by location (ie, skin, genitourinary, gastrointestinal tract) (Table 4).

Table 2
Follow-up Time

Group	Follow-up Time for Patients Who Were Alive at Last Contact			Total Cumulative Follow-up Time	
	n	Median, yr	Range, yr	n	Time, patient yr
Palifermin	247	7.9	.1-14.9	421	2256
Placebo	147	8.8	<.1-14.8	241	1302
Total	394	8.2	<.1-14.9	662	3557

Table 3
Baseline Demographic and Disease Characteristics (All Treated Patients)

Characteristic	Palifermin (n = 421)	Placebo (n = 241)	*P* Value
Age, mean (SD), yr	45.8 (12.5)	45.3 (12.3)	.808
Sex, n (%)			
Male	251 (59.6)	163 (67.6)	
Female	170 (40.4)	78 (32.4)	.040
Race, n (%)			
Caucasian	346 (82.2)	208 (86.3)	.167
Black	32 (7.6)	16 (6.6)	.646
Hispanic	27 (6.4)	13 (5.4)	.597
Unknown	16 (3.8)	4 (1.7)	.122
Diagnosis, n (%)			
Hodgkin lymphoma	77 (18.3)	59 (24.5)	.058
Non-Hodgkin lymphoma	311 (73.9)	159 (66.0)	.031
Multiple myeloma	21 (5.0)	15 (6.2)	.500
Acute lymphoblastic leukemia	3 (0.7)	1 (0.4)	1.000
Acute myelogenous leukemia	9 (2.1)	6 (2.5)	.770
Chronic lymphocytic leukemia	0	1 (0.4)	.364
ECOG Performance Status, n (%)			
0	290 (68.9)	174 (72.2)	.370
1	125 (29.7)	62 (25.7)	.276
2	3 (0.7)	3 (1.2)	.673
4	0	1 (0.4)	.364
Unknown	3 (0.7)	1 (0.4)	1.000
Presence of prior radiotherapy, n (%)	80 (19.0)	42 (17.4)	.615
Country, n (%)			
United States	255 (60.6)	162 (67.2)	.088
Australia	57 (13.5)	24 (10.0)	.176
Belgium	13 (3.1)	4 (1.7)	.264
Denmark	7 (1.7)	2 (0.8)	.499
France	51 (12.1)	23 (9.5)	.313
Germany	20 (4.8)	16 (6.6)	.303
Spain	6 (1.4)	2 (0.8)	.717
United Kingdom	12 (2.9)	8 (3.3)	.734

ECOG indicates Eastern Cooperative Oncology Group.

DISCUSSION

The results of this long-term follow-up study show no difference in overall survival and progression-free survival between palifermin- and placebo-treated patients with a hematological malignancies undergoing autologous HSCT. Furthermore, a comparable number of subjects in the palifermin and placebo groups developed secondary malignancies during the study, with no difference between the types (ie, hematological malignancies or solid tumors) or location of these secondary malignancies, suggesting that palifermin does not promote the development of secondary tumors. To our knowledge, this is the first long-term follow-up study of palifermin, and it shows that palifermin has no adverse effect on long-term disease outcomes in patients being treated for the prevention of OM while undergoing HSCT for hematologic malignancies.

Significantly more patients diagnosed with non-Hodgkin lymphoma and numerically fewer patients with Hodgkin lymphoma were included in the palifermin group compared with in the placebo group. We found no differences in outcomes despite the fact that in general, patients with relapsed non-Hodgkin lymphoma have a 3-year progression-free survival of 44% and patients with

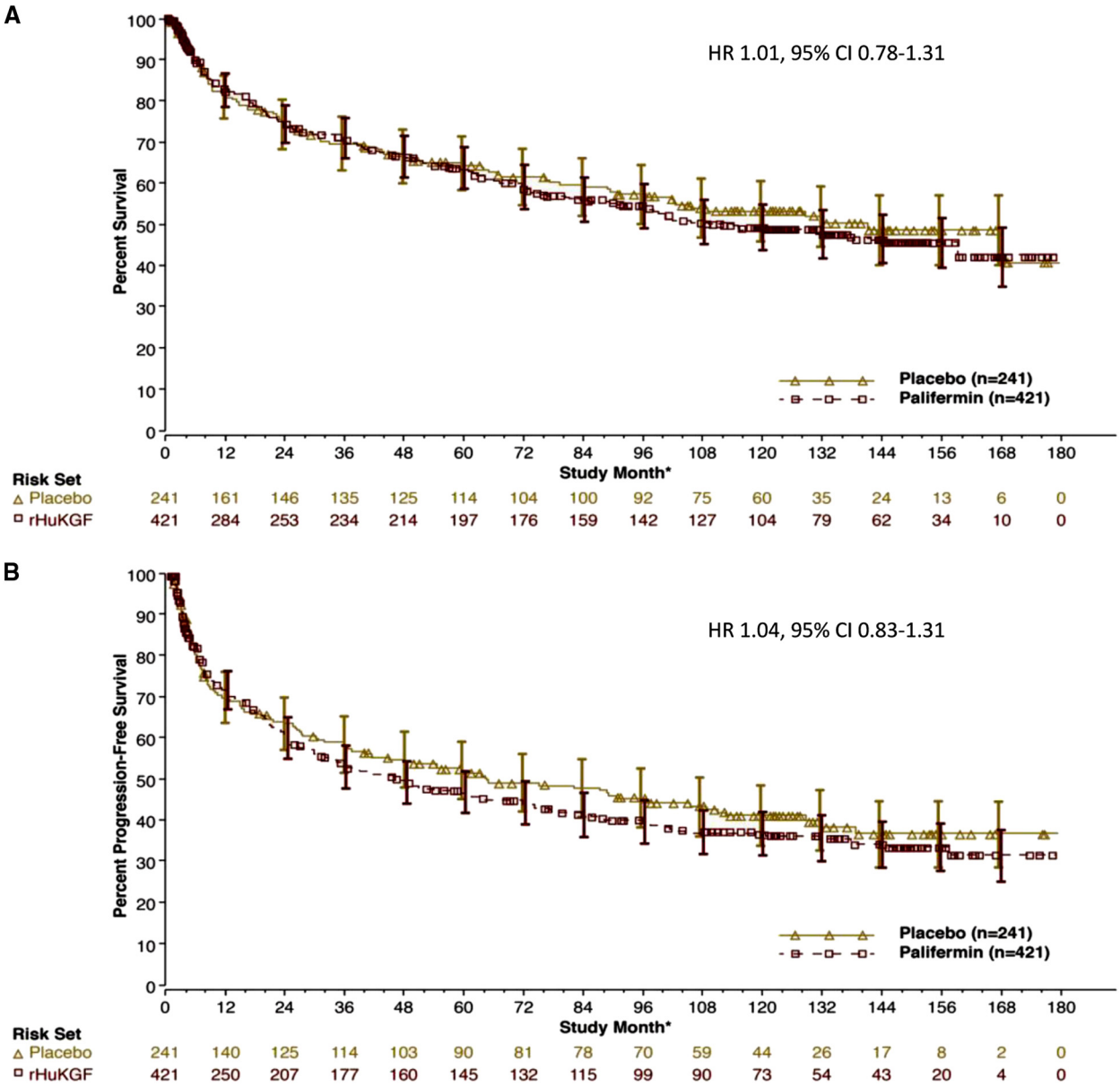

Figure 2. Unadjusted Kaplan-Meier curves for all treated patients for (A) overall survival, and (B) progression-free survival.

relapsed Hodgkin lymphoma have a better prognosis with a 3-year progression-free survival of 66% [19].

Our results are consistent with a small multicenter, nonrandomized, matched control study of 36 patients with a hematological disease treated with allogeneic HSCT, where no secondary malignancies were observed 3 years after cancer treatment in either of the palifermin or placebo groups [20]. In addition, our study extends the reported safety observation period from 3 years up to almost 15 years of patient follow-up.

Because palifermin is an N-truncated human KGF that can stimulate proliferation, differentiation, and survival of epithelial cells, the question was raised whether palifermin can drive tumorigenesis, inhibit cytotoxicity of cancer treatments, or promote the development of secondary tumors [21]. This study of up to almost 15 years follow-up provides the most relevant data from a clinical perspective, demonstrating that patients who are treated with palifermin have survival times comparable to patients treated with placebo and that they do not have a higher incidence of secondary malignancies.

An 18.5 years follow-up study of 800 patients who had received high-dose chemo/radiotherapy and autologous HSCT observed that secondary malignancies occurred at a median of 5.6 years (range, .1 to 14.8) after autologous HSCT, resulting in a 15-year cumulative incidence of secondary malignancies of 11% (95% CI, 5% to 18%) [18]. Based on this study, our study, which has an overall follow-up time of 14.9 years and a median follow-up time of 8.2 years, should have been able to adequately capture most of the secondary malignancies and observe an effect of palifermin, if any.

Some of the limitations of this study include the fact that the study was not prospectively designed as a noninferiority

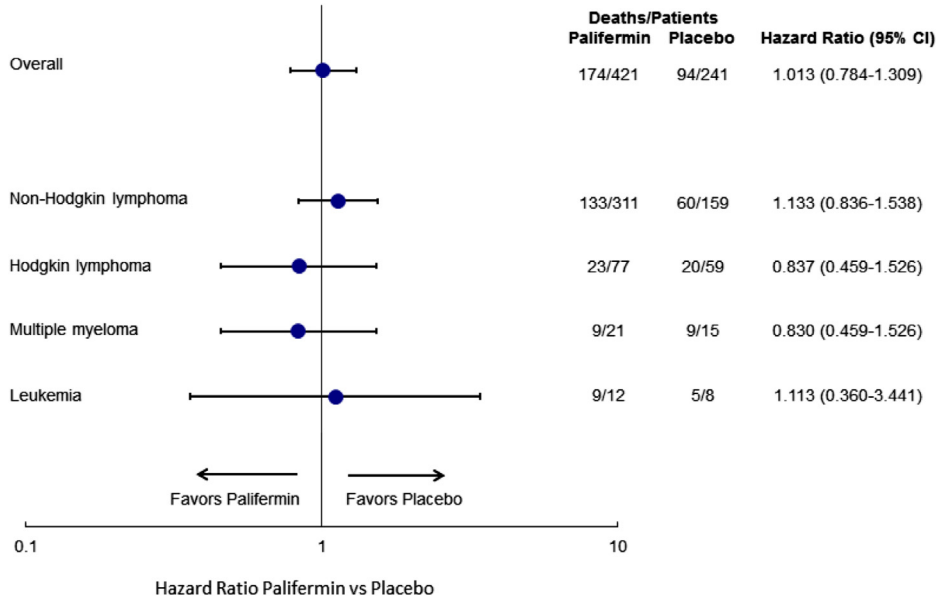

Figure 3. Forest plot of overall survival by disease subgroup.

study and that the parent studies were stratified for the factors influencing the incidence of OM. Thus, there may be a lack of prospective stratification in the parent studies for disease type or other important prognostic factors for disease progression and survival in this patient population. However, to account for the lack of prospective stratification, HRs were calculated using a Cox model adjusted for the prognostic factors. Another limitation is the lack of prespecified criteria for the evaluation of tumor response and disease progression, especially the accurate determination of the date of first disease progression. Finally, the lack of integration between the parent studies and the follow-up study, particularly early in the program, was also a limitation, as subjects enrolled in the parent studies were not required to participate in the follow-up study. One of the main strengths of this long-term follow-up study is that patients were enrolled and followed from multicenter, randomized, placebo-controlled studies.

In conclusion, after a follow-up time of up to 15 years (corresponding to 3557 patient years), comparable long-term safety outcomes were observed for palifermin- and placebo-treated patients undergoing autologous HSCT for hematological malignancies.

Table 4
Number of Patients Reporting Secondary Malignancies

Type of Malignancy, n (%)	Palifermin (n = 345)	Placebo (n = 198)
At least 1 secondary malignancy	46 (13.3)	22 (11.1)
Secondary hematological malignancy	23 (6.7)	11 (5.6)
Solid tumor	22 (6.4)	11 (5.6)
Skin tumor	10 (2.9)	6 (3.0)
Genitounirary tumor	6 (1.7)	3 (1.5)
Tumor in GI tract	4 (1.2)	3 (1.5)
Other solid tumor*	4 (1.2)	0 (0.0)
Other†	1 (0.3)	1 (0.5)

GI indicates gastrointestinal.
* Lung (n = 2), liver, and liposarcoma.
† Palpable lymph nodes, significant residual disease.

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Conflict of interest statement: T.K. and M.R. are employed by Sobi and have stock ownership in Sobi. M.L. and M.dC. are consultants or have an advisory role with Sobi. P.S. receives funding from Sobi.

Authorship contributions: All authors were involved in the conception and design in the study. M.L., M.R. and M.dC. collected and assembled the data. M.dC., P.S., and T.K. were responsible for data analysis and interpretation. All authors wrote the manuscript and gave final approval.

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